SCIENCE

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GENERAL PROBLEMS AND TENDENCIES IN CANCER RESEARCH[1]

AFTER the successful continuous transplantation of rat sarcoma and mouse carcinoma had shown that we possessed a method suitable for the study of the biology of tumors, and which promised a rich harvest of results, the decade following the year 1901 was to a great extent devoted to the study of propagated tumors rather than to the analysis of the first origin of tumors, although this latter problem had never been entirely neglected. Within recent years, however, much attention has been given to the origin of tumors. The so-called endemic occurrence of cancer which we observed in the case of cattle and rats, and which certain investigators noted in the case of mice and other animals, suggested to us sixteen years ago the possible significance of heredity as an etiological factor. Some years later, observations which we made in a mouse-breeding establishment in Granby confirmed this hypothesis; but it is only during the last six years, following the observations of Tyzzer and Murray, that our investigations, carried out in conjunction with Miss Lathrop, proved on a very broad basis the very great significance of heredity in the transmission of cancer in mice, the partial independence of the age and frequency factors, and the correlation between cancer frequency and structural and functional characteristics of the animal. The results of hybridization experiments which we carried out on a large scale indicate that in some crosses the tendency to a high

[1] An address before Section VIII. of the II. Pan-American Scientific Congress on January 5, 1916.

cancer rate may be dominant, while in some others the opposite tendency predominates, and in a few an intermediate result is obtained. Our experiments established for the first time the cancer rate for a number of different strains; each strain was followed through several successive generations and in each generation a large number of animals were observed. The resultant figures for the various generations of the same strain were usually in fairly close agreement. Animals belonging to such strains were used for hybridization experiments. The results of hybridization experiments which we obtained do not seem to be compatible with the view recently expressed that the tendency to cancer is a recessive character and that all results can be explained on such a basis.[2]

Of a different character is a problem in heredity first studied by E. E. Tyzzer. It is well known that some strains of mice are a favorable soil for a certain transplantable tumor, while other strains are not. In crossing a favorable and an unfavorable strain Tyzzer found conditions apparently incompatible with Mendelian principles. We obtained likewise in subsequent experiments with M. S. Fleisher, results similar to those of Tyzzer, and we suggested that the results might be explained by assuming the presence of multiple factors. The same interpretation may apply to the heredity of autochthonous tumors to which we referred above and in which also simple Mendelian proportions do not seem to exist.

These studies of the cancer incidence in various strains of mice and the methods used therein have, however, a much wider significance. On the basis of a thorough knowledge of the cancer incidence in certain families, and on this basis alone, will it be possible to analyze certain other factors in the etiology of tumors, and the understanding of these latter factors, as well as of heredity, will perhaps ultimately provide us with a rational basis for the prevention of cancer. Without a thorough knowledge of heredity, conclusive results as to the significance of other factors could not be expected. Acting on this principle, we found that castration in sexually mature mice at the age of three to eight months reduces the cancer rate in a very pronounced way. Prevention of pregnancy, while it still has some effect in reducing the cancer rate, as we found several years ago, has very much less significance than castration.

These results and some additional ones to be mentioned shortly permit us to classify the causes of tumors into two main divisions, internal and external ones. Heredity belongs to the former class. The point of attack of these hereditary factors we do not yet know. In some cases, they may perhaps stand in relation to some other internal factors, which are in all probability of significance in certain cases. I refer to the spontaneous parthenogenetic development of the egg within the ovary and elsewhere in mammals, a process which, according to our findings in the guinea pig, is not a rare occurrence, and may even normally proceed to the formation of the anlage of the central nervous system. To this class of factors may also belong developmental errors which were already suspected by Cohnheim and which as we know may appear as inheritable mutations in various groups of animals.

The external factors may be further divided into chemical and mechanical, and both may be derived either from within the body or from the outside world. As an example of a chemical factor originating within the body, we may cite the great importance of the internal secretion of the

[2] Maud Slye, *Interstate Medical Journal*, XXII., July, 1915, p. 692.

corpus luteum in the origin of cancer in mice to which we referred above, but other internal secretions will probably be found to be of similar significance. External mechanical factors can be recognized in the well-known effect of chronic irritation. How far certain parasites, especially those in the class of vermes and insects, produce cancer through chemical and how far through mechanical means is not certain. Previous observations in man in the case of cancer of the bladder caused, directly or indirectly, by bilharzia, and especially the recent experiments of Fibiger make it, however, quite certain that such parasites may be the cause of cancer. It is likewise uncertain how far Roentgen-ray cancer, frequent in Roentgen-ray operators, and also apparently experimentally produced in a few rats by Marie, is due to ulceration subsequent to exposure to or to the direct stimulating action of the rays. In some cases perhaps chemical and mechanical factors may cooperate in producing tumors; the efficiency of such a combination in calling forth tumor-like formations has been shown by us in the case of deciduomata of the uterus, which we produced experimentally, a new formation which we included in a class designated as transitory tumors.

There are observations on hand which indicate that growth stimuli may be especially active in animals with a hereditarily determined tendency to cancer. Such an observation we made in the case of a cancer in a mouse belonging to a family rich in tumors, where ulceration of the skin near an adenoma of the mammary gland led to the development of an epidermal carcinoma. Further systematically conducted experiments in this direction might lead to interesting results.

It is, however, not probable that in order to obtain the production of cancer there must be a definite quantity of prerequisite internal factors. On the contrary, there is some evidence on hand which makes it probable that internal and external factors may vary in inverse ratio, and that if the external factors are quantitatively very strong, the quantity of internal factors may be reduced.

If we survey briefly the various types of growth reactions known in vertebrates, we may perhaps, according to the character of the stimuli, which are usually in each case the first members in a complicated reaction chain, and according to the character of the systems on which they act, provisionally distinguish the following types:

1. Various stimuli act for a short time on complex systems, the egg-cells, and lead to a long chain of growth phenomena which ultimately cease. The experiments in artificial parthenogenesis of Jacques Loeb led to a very far-going analysis of these phenomena.

2. Defects lead to a chain of growth phenomena, which are of a temporary character, and which come to a standstill after a certain quantity and kind of new-formed tissue has more or less completely filled out the defect.

3. Chemical substances stimulate the growth of certain tissues to which they bear a more or less specific relation. These growth phenomena come to a standstill with the activity of the stimulating substance or very soon afterwards (corpus luteum and mammary gland).

4. A combination of factors 2 and 3 may lead to tumor-like growth phenomena when either factor alone would cause only a slight proliferation. Here again the effect is temporary (experimental deciduomata of the uterus).

5. Chemical (fat soluble?) bodies which do not show a specific relation to the organs affected stimulate various tissues to a temporary proliferation; fat soluble stains

(Bernhard Fischer and others) and ether (Reinke) are substances that under certain conditions seem to exert a stimulating effect.

6. Chemical and mechanical factors produce with the aid of a large quantity of internal factors, or in certain cases apparently without such aid, an increase in cell proliferation that persists after the stimuli have ceased, which is permanent, potentially of unlimited duration in contradistinction to the temporary reactions mentioned above. This is the cancerous reaction with which all or at least the large majority of the mammalian tissues may respond. Neither potential immortality—some, or perhaps all, somatic cells are potentially immortal —nor the power of continued proliferation, which in all probability even certain ordinary somatic cells possess, is characteristic of this reaction, but rather the increase in proliferative power, and furthermore the permanency of the reaction in response to a temporary, non-permanent stimulus. We have then to assume that a labile cell-system which responds to temporary stimuli with a temporary reaction is transformed under the influence of certain stimuli, and often with the aid of hereditary factors, into a stable system which shows a greater proliferative power than the labile system. The stimulus thus brings about merely a transformation of the cells into a new kind of cell-system, which proliferates indefinitely at a more or less increased rate. Such a transformation may be called a mutation.[3] Inasmuch as all, or the large majority of all body cells are liable to this change, they must have from the beginning in their organization a mechanism that provides for the possibility of such a mutation.

[3] We would have to deal in this case with a mutation, not in a germ cell, but in a somatic cell. For a more detailed discussion of this problem *cf.* Leo Loeb, "Germ Cells and Somatic Cells," *American Naturalist,* Vol. 49, 1915, p. 286.

According to this conception, we must then assume that all or most cells have potentially two equilibria, the normal one and the cancerous; they begin life with the normal equilibrium, but under the influence of certain stimuli, with or without the cooperation of hereditary factors, they are transferred to the cancerous equilibrium.

Cells in the normal equilibrium react to stimuli in the manner indicated above (types 1 to 5); ultimately they return invariably to the normal equilibrium after the stimulus has ceased to act. Cancerous cells, on the other hand, may perhaps be exterminated, but they are not known to return to the normal equilibrium.

There is, however, an alternative to this conception which would eliminate the necessity for assuming a new equilibrium for cancerous proliferation, an assumption for which naturally no analogy can exist. If we assume that an external agent associated with the cell, rather than a physico-chemical mechanism within the cell, produces the cancerous proliferation, the latter would no longer represent a unique condition, but would be a special application of one of the types 3 to 5, in which, however, the stimulus would act incessantly. Such a stimulus could be supplied through multiplying microorganisms which essentially represent constantly newly formed external chemical stimuli. Such microorganisms would not be identical with bacteria causing various ordinary infectious diseases. As we have shown at an early stage of our investigations, cancer among animals is not infectious in the sense in which certain other diseases are infectious. We could feed tumor tissue to normal animals or keep normal animals in the same cage with cancerous animals without a transfer of the disease taking place; neither could Ehrlich produce cancer in young mice which were suckled by cancerous animals. But this does not

exclude the possibility that certain other organisms might play a certain rôle. We know that microorganisms can call forth cell multiplication in plants and animals. In plants, certain bacteria can produce, as has especially been demonstrated in the case of the crowngall by Erwin F. Smith, tumor like proliferation—a result depending in this case not merely on the kind of stimulus, but also on the particular system on which the stimulus acts. In this connection we might also mention a number of extremely interesting cases in which various investigators saw the transformation of normal into cancerous tissues, subsequent to contact with cancerous tissue of another kind, but in the same individual. I referred above to an observation of this character in which we found skin to become cancerous under the influence of an adenocarcinoma of the mammary gland. Similarly, in contact with carcinoma, connective tissue may become sarcomatous. Such tumors we called combination contact tumors. In such a carcinosarcoma in a Japanese mouse which we studied experimentally, we found that the carcinomatous and sarcomatous components followed the same variation curve of growth energy in succeeding generations. This suggests the identity of the agent which causes the proliferation of both tissues and the dependence of the variation in growth upon the variation in the activity of the agent. The agent transferred from one tissue to another might be a chemical substance—an explanation first suggested in the case of the sarcomatous transformation of the stroma by Ehrlich and Apolant—or it might be a microorganism. Even under normal conditions there are indications which point to a chemical influence exerted by one tissue upon another. In this manner we interpreted the difference in cell activity in the connective tissue of the mucosa in certain organs near the epithelium on the one, and near the submucosa on the other hand. The different effect exerted by the tissues of different individuals upon the activity of the fibroblasts of the host also points to such a conclusion (different effects of auto- and homiotransplantation).

The very important results of Peyton Rous are worthy of especial consideration. This investigator, working with fowls and employing methods which in the case of mammalian tumor had not led to positive results in the hands of earlier investigators, was able to separate by filtration and other means the causative agent from the sarcoma cells with which it was associated. In this case, we might have to deal either with filterable microorganisms, or again with chemical substances. If we accept the latter alternative, we would have to assume that the same substance that initiated the cancerous cell proliferation in normal cells would, after the change has once been accomplished, be perpetually newly formed within the proliferating cells. This condition would in some respects be comparable to an autokatalytic process.[4] The cancerous equilibrium would represent a condition in which this growth substance is either produced in a larger quantity than it exists in normal cells, or is entirely formed de novo. It seems furthermore that no antibody is produced in the body-fluid against this substance. These substances do not seem to be separable from the cells in all fowl tumors, and the kind of fowl tumors in which a separation can not be accomplished behave in this respect like the mam-

[4] Certain analogies between growth curves and autokatalytic processes have formerly been pointed out by Jacques Loeb, W. O. Ostwald and T. B. Robertson. In the case of fowl tumors we would have in addition to deal with the new formation within the tissue cells of a substance carried to the tissues from the outside.

malian tumors. We would have to assume the existence of different substances of this kind, and different substances always call forth a specific activity of connective tissue cells resulting in the reproduction of the original kind of tumor, and stimulating endlessly the production of the same specific substance within the fibroblasts. Just as in the case of the corpus luteum substance which is responsible for the production of deciduomata, the cooperation of a mechanical factor seems to be essential for the stimulation of tumor growth in fowl. We would most probably have to give this interpretation to these phenomena if the observation of Casimir Funk, according to whom an alcoholic extract of the tumor contains the active agent, could be confirmed in a larger number of cases. If this should prove correct, we may expect to find corresponding conditions in mammalian cancer. A study of heredity in cancer of the fowl would close this chain of investigations, and with the analysis of internal and external factors in cancer already on a solid foundation, we could then conclude that the causes of cancer in their main outline have been satisfactorily analyzed. Of course underneath this first plane of causes there are connections which extend further into fields where they meet with other factors determining cell and tissue life in its dependence upon physical and chemical laws, and thus we are led into deeper planes of causation. But here the problems have become identical with those of general biology, the laws governing cell division and ameboid movements in cancer cells not differing from those of other cells.

In this connection a few words concerning the definition of cancer might not be out of place. It might indeed be assumed that a definition of cancer satisfying past and future research is one of the essential requirements for the fruitful pursuit of investigation. On the contrary, I believe that at the present stage of investigation progress may be retarded through premature rigidity in defining cancer, and especially through insisting on the proof that secondary tumors originate from transplanted cells. In the case of sarcoma of the rat and mouse, this proof has so far been supplied only in the rat sarcoma of the thyroid found in Chicago, and is merely based on analogy in the case of the large majority of other sarcomata. Since it has now been shown that in sarcoma of fowl an agent associated with the tumor, but separable from it, may just as well give origin to new growths, we may well hesitate in excluding from consideration new formations which in all probability under certain conditions have their origin in transplanted cells, while in other cases they may perhaps be propagated through an agent associated with the tumor. I refer here especially to the so-called lympho-sarcoma or small round cell sarcoma of dogs which, after transplantation in dogs, apparently grows from the transplanted cells (Sticker, Ewing and Beebe, and L. Loeb), while in the fox, according to von Dungern, the tumor cells are composed of host tissue. May we not, in case von Dungern's view should prove correct, have to consider the possibility that the transplanted dog cells perished in the foreign species, and that the associated agent stimulated the host cells to proliferation?

With the factors which we have already analyzed—factors of heredity, of internal secretion, of external, chemical and mechanical stimulation—we are in a position to control to a great extent the cancer rate in certain species of animals. As we said, we can not yet exclude with certainty the other alternative, namely, microorganisms, as an additional causative factor.

After so many futile attempts to establish a direct proof of their presence, further

efforts of this kind do not appear promising at present. There seem, however, still other ways open through which one may approach this problem in an indirect manner.

To decide between the two alternatives which we mentioned does not only concern cancer research in the more restricted sense, but is of the greatest importance for general biology. In return for much that it received from neighboring sciences, cancer research has given something important to biology; the serial endless experimental propagation of tumors has enriched biology with a valuable instrument of research and new outlooks on the life and character of somatic cells have been gained. We may briefly mention the following facts established or very strongly suggested: In the course of our early transplantations, we found that the energy of tumor growth can be experimentally increased as well as decreased. Ehrlich explained the increase as due to a selection of rapidly growing tumors; we, however, believed from the beginning that it was partly produced by a mechanical stimulation of the tumor cells and in addition was possibly due to chemical stimulation caused by the transfer into a new host with a different constitution of the body-fluids; in some cases perhaps processes of immunity may also enter into this phenomenon.

In conjunction with M. S. Fleisher, we noted that chemical bodies which inhibit tissue growth at a certain period in the life of tumors do not have this power at other periods. Especially are they powerless in the case of very young tumors, an observation confirmed by Keysser. But we found that such early injections produce an immunization against the later action of these substances. The proof thus given that an immunization takes place against substances (and apparently also against physical agencies) inhibiting tumor growth is, as we pointed out on previous occasions, of great importance in our attempts to arrive at a rational treatment of cancer. Our experiments suggest, furthermore, very strongly that this immunity is of a twofold character, that it originates in the host as well as in the tumor cells themselves; that this cell immunity can be transferred to a certain number of later cell generations and is to some extent specific for the substance which had called it forth. While our results, based on the observation of a very large number of animals, strongly suggest these latter conclusions, we nevertheless think it desirable to add new evidence in order to guard against a complication with variable factors.

Are we in all these cases dealing with indirect actions on the cells and with direct actions on accompanying microorganisms, or with direct actions on the cells? We rather incline to the latter view and we would suggest that an increase in chemical activity in the tumor cells—an increase perhaps restricted to certain activities—renders the latter a much finer balance in their response to certain environmental conditions through variations in growth energy than are the normal tissue cells.

As we pointed out in 1901 on the basis of Morau's and our own experiments, cancer cells are potentially immortal in the same sense in which Protozoa and germ cells are potentially immortal. All, or at least the large majority of all normal tissue cells are potentially cancer cells, and we may therefore with full justification conclude that ordinary somatic cells are likewise potentially immortal. Like the majority of tumors, they can not be indefinitely propagated in other individuals of the same species because of the injurious action of what we may term homoiotoxins. On the other hand, thanks to their increased growth energy and perhaps a lessened sensitiveness

to homoiotoxins, the cells of certain tumors can overcome the injurious conditions existing in other individuals of the same species and be propagated indefinitely. Tumor cells and ordinary tissue cells do not differ in potential immortality (as Bashford and others assumed), but in the intensity with which they proliferate and in their destructive power.

Of equally great biological interest are the defensive reactions called forth in the host through the growth of the tumor cells. As one of the most important results, we may here state that no immunity seems to be produced through tumor growth in the animals in which the tumor originated. We found that in the case of rat and dog tumors, cells remained alive and grew after transplantation into the animal in which they originated, while they died in other individuals of the same species. Tyzzer found the same to be true in the chicken, and Haaland and Fleisher and ourselves in the mouse. Haaland's experiments suggested, furthermore, that the autochthonous tumor could not act as antigen and by proving in addition that this tumor does not neutralize immune substances, our experiments prove the correctness of Haaland's suggestion that against an autochthonous tumor no immunity can be produced. The greater significance again attached to the study of animals in which tumors originated in contradistinction to bearers of experimental tumors, is one of the characteristic tendencies of recent cancer investigation, and it is of interest in this connection to note that our experiments indicate that animals with autochthonous tumors are a better soil for the growth of other spontaneous tumors than normal animals.

While therefore in the organism in which the tumor originated usually no reaction takes place against tumor cells, reactions do take place after transplantation of tumor cells into other individuals. These reactions are essentially of a similar character in the case of tumors and of normal tissues. Again correlation between the behavior of normal and of cancerous tissues has proven fruitful of results in this case. After autotransplantation of a piece of normal tissue, it may in the same way as a piece of tumor, at least in the case of certain tissues, apparently live indefinitely, while after homoiotransplantation, as we observed, the tissues die as a result of the attack by lymphocytes and through the influence of fibroblasts of the host which produce dense fibrous tissue which in turn strangulates the foreign cells. There is a possibility that the strange body fluids may also directly interfere with the metabolism of certain transplanted tissues to such an extent as to severely injure them. After heterotransplantation the indirect injurious action of the body fluids, which are unsuitable for the metabolism of the transplanted cells, is more pronounced and leads to the early death of the transplanted cells. We found in the case of skin under these conditions no noticeable activity on the part of the lymphocytes and fibroblasts. J. B. Murphy, however, recently showed through very ingenious experiments that in the case of heterotransplantation also lymphocytes, under certain conditions, may be of importance as a defensive mechanism of the host.

It has likewise been shown by such investigators as Burgess, DaFano, Baeslack, Rous and J. B. Murphy, that in the case of tumors against which an immunity becomes established, lymphocytes sometimes, in conjunction with other leucocytes, play a distinct rôle in the destruction of the tumor tissue. This holds good in the case of tumors already established. If immunity is produced before the transplanted tumor has united with the host tissues, the ingrowth

of fibroblasts and blood vessels into the transplanted tissue may, according to Russel and Woglom (in the case of tumors) and Peyton Rous (in the case of embryonic tissues) be delayed or else diminished in amount. However, even in the latter case the defence of the organism against the foreign tumor cells may principally consist in an attack by lymphocytes and other leucocytes (E. E. Tyzzer).

As the most probable explanation for these phenomena, we have proposed the following theory:[5] The mutual chemical incompatibility of the body fluids of one individual and the tissues of another, which we could especially clearly demonstrate after homoiotransplantation of pigmented skin, leads to changes in the metabolism of the tissues, resulting in the production of homoio- and heterotoxins, which if they do not exceed a certain strength, disturb the normal functions of the transplanted tissues to some extent without, however, interfering seriously with their life. But the abnormal products formed attract the lymphocytes and in certain cases also other leucocytes, and alter the reaction of the fibroblasts, which latter are induced to produce dense fibrous tissue. If the poisons become more active, they may directly injure tissues to such an extent that growth and life become impossible.

These conclusions, as we believe, also throw light on so-called chronic inflammatory processes of various organs where a changed metabolism of the cells, and perhaps also poisons produced by microorganisms, may induce fibroblasts to form fibrous bands and attract lymphocytes, thus leading to processes of cirrhosis. In a similar way, in the case of tumor immunity, which, for instance (as Clowes and Gaylord have shown), exists in the case of the retrogression of tumors, substances produced as a result of immunization and which circulate in the body fluids alter the metabolism of the tumor cells, which in turn influence the activity of the lymphocytes and fibroblasts in a way similar to normal tissues in a strange host. This theory correlates the immunity against tumor and tissue growth with the immunity against certain substances and non-growing foreign cells. We have also in the former case to deal with the production of immune substances, which, however, in the case of homoiotransplantation, are usually not such that they directly destroy the foreign tissues, but merely lead to an alteration of their metabolism and to the production of substances which change the behavior of the host cells. We no longer need to assume a primary tissue alteration following the homoiotransplantation.

It remains for further investigations to decide to what extent the presence of foreign tissue leads to the direct production of what we could call primary homoio- and heterotoxins as the result of the interaction between the preformed constituents of the body-fluids and the foreign cells, and to what extent it leads to the production of secondary homoio- and heterotoxins—the immune substances—as the result of immune reactions. At present it appears probable that both these substances play a rôle. In vitro the toxicity of body fluids of foreign species is apparently not very marked, as we, as well as Lambert, found. The toxicity is certainly less than we should expect, considering the fate of tissues after heterotransplantation. We must, however, take into account the fact that the amount of body fluid and especially of toxin acting on the tissue in vitro, is extremely small as compared with the quantity acting in the

[5] Leo Loeb, "The Influence of Changes in the Chemical Environment on the Life and Growth of Tissues," *Journal American Medical Association*, Vol. 64, February, 1915, p. 726.

living body, and that this reduction in the quantity of body fluid is very much greater than the reduction in the quantity of tissue. Furthermore, in the body the fluid in contact with the tissue is constantly renewed and the old fluid is eliminated. In vitro the fluid remains relatively constant. There exists also the possibility that the action of the body fluid is a complex one in vivo in a way similar to the complex action after homoiotransplantation. In the case of both types of substances (those preformed and those produced through immunization), we are able to point to analogous substances existing elsewhere, namely, the preformed species-specific tissue coagulins, which play a rôle in the blood coagulation, and the secondarily, artificially produced antibodies of various kinds. It also remains further to be determined, how far the metabolic products of foreign cells exert a direct influence upon each other and how much of this effect is dependent upon the interaction between cells and foreign body fluids.

In addition to the effect of toxic substances, mere lack of common food-stuffs can also retard tumor growth, as the retarded growth of transplanted tumors in pregnancy and the feeding experiments of Moreschi, Peyton Rous, Beebe, Sweet, Corson White, and Saxon, Robertson and Burnett have shown. Other substances apparently stimulate tumor growth (Robertson and Burnett). Whether an immunity caused through the lack of specific substances—in contradistinction to the common food and growth stuffs of cells—whether, in other words, an athreptic immunity, as Ehrlich called it, exists, however, is very doubtful. Such an athreptic immunity certainly would not explain the phenomena referred to above, as especially the experiments of Uhlenhuth, Haendel and Steffenhagen, Tyzzer and Levin have shown.

In the retarded cancer growth in pregnancy especially we do not have to deal with a scarcity in specific growth substances, particularly in hormones, as Ehrlich supposed, but with a shortage in the ordinary substances required for the building up of cells. On the contrary, it seems to us very probable that certain hormones which circulate during pregnancy may be of advantage to tumor growth, and that these two antagonistic factors—deficiency in ordinary building material and presence of special hormones—may preponderate unequally in different cases and thus the difference in the effects on tumor growth which certain investigators found in pregnancy may be explained.

In connection with the studies in metabolism to which we have just referred, we may look forward to interesting results through further analysis of the chemical constitution of tumor tissues.

I am, however, inclined to regard the differences so far found between normal and tumor cells in a similar light, as differences observed in the case of mitotic division in normal and tumor cells, both probably being the result and not the cause of the changes in the growth energy characteristic of tumor cells.

Having arrived at the end of our survey, we must confess that much remains still to be done before these investigations can in any way be considered near completion. On the other hand, I believe that I have indicated that there are yet other ways open for further attack upon the problems of cancer and tissue growth, and I hope also that I have been able to convey the impression that the work of so many investigators in this field has not been in vain, and that not only this special branch of science has been built up, but that also biology

and pathology in general have been stimulated and enriched as the result of their labors.

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THE UNITED STATES FISHERIES BIOLOGICAL STATION AT BEAUFORT, N. C., DURING 1914 AND 1915

THE laboratory of the U. S. Fisheries Biological Station at Beaufort, N. C., has been open for investigators each summer for the past seventeen years. Below is given a brief summary of the various activities of the station during the years 1914 and 1915.

The many improvements and repairs effected during the past two years have contributed materially to the appearance of the small island on which the station is located, and to the working efficiency of the laboratory. The grounds were graded and covered with a coat of black top soil in which grass was planted and grown with success. An additional breakwater was built, the terrapin pounds were enlarged, and a fish pool and tide pool were constructed. The cedar post foundation of the main building was replaced by brick piers, the old coal house was rebuilt into a boat house, connected with marine boat ways, and a new coal bin connected with the power house was constructed. About 338 square feet of concrete walks were laid. Porches were constructed across the ends and south side of the dormitory rooms. These added much to the appearance of the building and the comfortableness of the bed chambers. A library room and a small laboratory have been provided on the lower floor of the main building. The power house has been equipped with a salt-water pump of such ample dimensions that the 10,000-gallon salt-water tank can be filled in about one seventh of the time previously required, with a consequent saving in labor and fuel. A new projection and micro-photographic apparatus was added to the laboratory equipment.

Under the direction of the librarian of the central office of the Bureau the library has been systematically arranged and catalogued. The number of volumes has been increased by both purchase and voluntary contributions of publications on biological subjects from various authors and institutions.

Most of the investigators who were employed during the past two years had been with the laboratory before, and continued lines of work begun previously. Professor H. V. Wilson, of the University of North Carolina, was at the laboratory for a short time during both summers. He continued the study and identification of the Albatross-Philippine sponge collection. Nearly all the forms studied differ in more or less important respects from described forms and most of them will be published as new species or varieties.

Dr. S. O. Mast, of Johns Hopkins University, was with the laboratory during the summer of 1914 and continued his studies of the previous season on the changes in shades, color and patterns in fishes, with especial reference to the flounders, *Paralichthys* and *Ancylopsetta*. He also made some observations on the behavior of *Fundulus majalis* in tide pools.

Dr. Mast was unable to demonstrate that adaptation to background in the above-named flounders has any biological value. Experiments, however, indicate that there is in flounders a tendency to select bottoms which harmonize with their skin in color as well as in shade. It was also shown that flounders do not compare their skin with the bottom in the process of adaptation, but that this is regulated solely by the effect of light received by the eyes from above and by its reflection from the bottom. The results of Dr. Mast's work also indicate that the fusion rate of images on the retina for flounders and for man is the same.

With reference to the behavior of *Fundulus majalis*, Dr. Mast's observations indicate that this fish has a sense of direction probably somewhat similar to certain birds. It was noticed many times that when a school of these fish was left in a tide pool as the water fell they left the pool and crossed a sand bar, continuing their flops toward the sea until water was reached, and seldom making the mistake of coming out on the wrong side of the pool.